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Synthesis, Characterization and Biological Evaluation of Oxazolone Derivatives

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ABSTRACT

A series of six 4-aryl Benzelidene-2-phenyl-5- oxazolone derivatives were synthesized by condensation of aromatic aldehydes with N-benzoyl glycine (Hippuric acid) in the presence of sodium acetate and acetic anhydride at room temperature in ethanol. Six of the compounds are new derivatives. The structures of the compounds were evaluated based on 1H-NMR , IR and FTIR methods and by elemental analysis. .All the derivative compounds prepared were tested for their antimicrobial activity by disk diffusion technique. Test organisms: Bacteria like Staphylococcus aureusMTCC 7443 and Salmonella typhimuriumMTCC 733 Fungi like C.albicans and A.flavus The results were compared with those of the standard 0.5% Ciprofloxacin. The derivatives with Salicylaldehyde and cinnamaldehyde were showed excellent activities against E. coli. and Staphylococcus aureusMTCC 7443 : than Salmonella typhimuriumMTCC 733 bacteria. It also showed reasonable activity withFungi like C.albicans than A.flavus

Keywords: *N-Benzoyl Glycine, Aromatic aldehyde, Oxazolones , Antibacterial Activities*

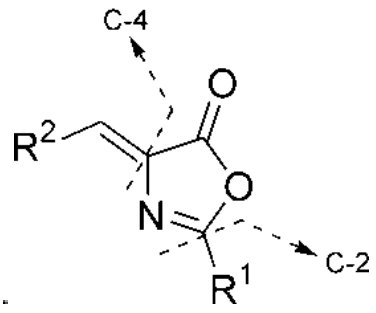
I. INTRODUCTION

For many decades, increasing resistance against human pathogens that cause serious infections is one of the main topics of interest for medicinal chemists. Many medicines were developed against bacterial infections. Since many decades, active heterocyclic compounds are one of the main topics of interest for the medicinal chemists as it displays a number of pharmacological activities.

Mostly Nitrogen- Sulphur- and Oxygen- containing five- and six-member heterocyclic compounds like oxazolones have enormous significance in the field of medicinal chemistry and these are class of small heterocyclic compounds which have acquired more importance in recent years due to their pharmacological activities.

Oxazolones are five membered heterocyclic compounds containing nitrogen and oxygen as hetero atoms. The C-2 and C-4 positions of oxazolone are responsible for their various biological activities such as analgesic[1], anti-inflammatory, antidepressant[2], anticancer, antimicrobial[3], antidiabetic[4] and antiobesity Oxazol-5-ones contain correspondence numerous reactive sites allowing for a diverse set of possible modifications. Hence we aimed to design novel derivatives containing a variety of oxazolone derivatives with structural variation at C-2 and C-4 positions were synthesized and evaluated anti-microbialactivities.

Figure 1: Structure of Oxazalone



II. MATERIALS AND METHODS

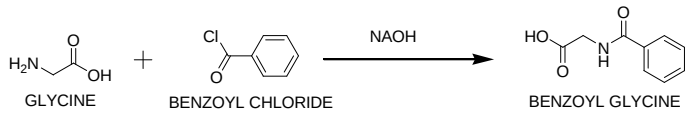
All the chemicals were of synthetic grade and commercially procured from SD fine Chemicals Ltd. Mumbai, India. Melting points were recorded on Electric melting point apparatus and are uncorrected. IR spectra were recorded on FT-IR 8400S, Fourier Transform (SHIMADZU) Infrared spectrophotometer using KBr disc method. The 1H-NMR spectra were recorded in $CDCl_3$ on AVANCE 300MHZ NMR Spectrophotometer using TMS as an internal standard. Thin layer chromatography analyses were performed on pre-coated silica gel plates (G 350, Merck).

Procedure

SCHEME 1: General Synthesis of Phenyl Glycine or Hippuric acid from Glycine

Glycine (10gm) is first dissolved in 10% sodium hydroxide solution (100ml) and reaction mixture is kept in ice cold water and benzoyl chloride (21.6ml) is added drop wise with continuous stirring after addition of all benzoyl chloride pH of the reaction mixture is adjusted to 2-3 with concentrated HCl and the precipitate of phenyl glycine obtained.

SCHEME -1



SCHEME:2

Preparation of Different Oxazolones:

Hippuric acid(0.01m), acetic anhydride(0.04m), sodium acetate(0.01m), aromatic aldehyde(0.04m), are taken in a conical flask and the reaction mixture is heated for 15mins on heating mantle then the reaction mixture is cooled for 5mins and 2-3 drops of ethanol is added and the ice cold water is poured into the reaction mixture to get the precipitate of oxazolones.

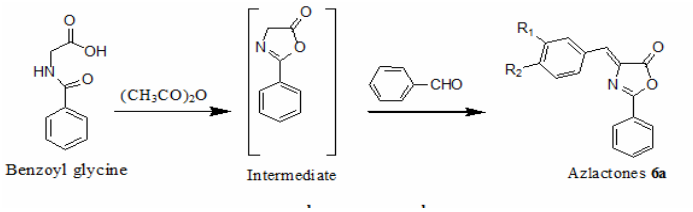
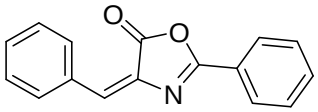
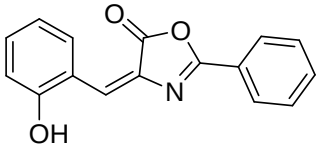
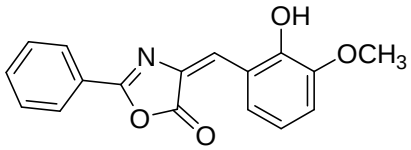
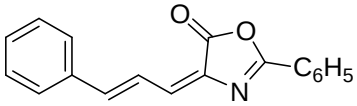


Table 1: Physical Constants Data of Synthesized Compounds

SL NO	STRUCTURE	MOLECULAR FORMULA (mol.weight)	% YIELD	MELTING POINT IN °C
2a		$C_{16}H_{11}NO_2$ (249)	70	170
3a		$C_{16}H_{11}NO_3$ (261)	65	167
4a		$C_{17}H_{13}NO_4$ (295)	54	192
5a		$C_{18}H_{13}NO_2$ (275)	75	180

1. AntibacterialAssay: **Determination of Antimicrobial activity;** 100 µl Inoculum of test cultures was inoculated on Muller Hinton Agar plates (90 mm) for bacterial .Test compounds (10µl, 10 mg/mL), and ciprofloxacin (2.5 µl, 1 mg/mL) were impregnated on 6mm sterile Whatmann No. 1 Disks for bacterial cultures. Test compounds and standard disks were placed on Agar plates.The plates were Incubated @ 35 ^{0}C for 24-48 hrs and observe for zone of inhibition around the disk.

2. Inoculum:

Cell suspension prepared from cultures grown on Trypticose soya broth adjusted to 1-2 x 10^5 cells/mL. For fungi spore suspension of the cultures grown on Sabouraud Dextrose agar was adjusted to 1-2 x 10^5 cells /mL.

Test concentrations: drug concentration prepared Test compounds: 10 mg/mL in 10% DMSO in Methanol. Control: 10% DMSO in Methanol.

III. RESULTS AND DISCUSSIONS

Chemistry: Oxazolone derivatives were synthesized by condensation of substituted aromatic aldehydes with Hippuric acid using sodium acetate as a catalyst in ethanol at room temperature. The synthesized compounds were scaled for yield and purified by recrystallization with suitable solvent system. The purified compounds are identified/characterized by following methods melting point, solubility, thin layer chromatography and results were listed in table 1, the synthesized compounds were characterized using different spectroscopic techniques. The IR spectrum showed characteristic band of carbonyl group at 1772cm^{-1} and C=N at 1352 cm^{-1}. $_1$H-NMR spectrum showed characteristic pattern of peaks. The methyl protons appeared in the region of 3.84 ppm, whereas the aromatic protons appeared at 6.89–8.12 ppm.

Antibacterial Activity:

All the compounds 2a to 5a were tested for their antibacterial activity against B**acteria** *Staphylococcus aureus* MTCC 7443 &*Salmonella typhimurium* MTCC 733&**Fungi** *C.albicans,A.flavus and* E. coli, by **disk diffusion technique** .But many people have reported by zone of inhibition method against E.Coli B. subtilis, B. subtilis, S. aureus, P. aeruginosa, and K.pneumoniae [6]. The results were compared with those of the standard 0.5% Ciprofloxacin. Compounds (3a) showed excellent activities against only for E. coli, which is very difficult to treat with traditionally used antibiotics. The most active compound against E. coli was compound (3a) against all other derivatives. All the compounds from 2a to 5a showed very low and nil activity against B**acteria** *Staphylococcus aureus* MTCC 7443 &*Salmonella typhimurium* MTCC 733&**Fungi C**.*albicans,A.flavus.*

Test Organisms	**Test Compounds**	**Concentration (µg/disk)**	**Zone of inhibition**
E.Coli	2a	200	7
	3a	200	18
	4a	200	10
	5a	200	2
	Ciproflaxacin	2.5	20
Staphylococcus aureus	2a,3a	200	3
	4a,5a	200	No inhibition
Salmonella typhi	2a,3a	200	No inhibition
	4a ,5a	200	No inhibition
	Ciproflaxacin	2.5	15.00 ± 0.00
C.albicans	2a	200	No inhibition
	3a	200	No inhibition
	4a	200	Inhibition but Not measurable
	5a	200	
	Crystal Violet	100	21.00 ± 1.00
A. flavus	2a to 5a	200	No inhibition
	Crystal Violet	100	25.00± 2.00

IV. CONCLUSION

It is concluded based on the biological activities of the synthesized oxazolone derivatives, it could be concluded that they are therapeutically active antibacterial agents, among all synthesized compounds the compound (3a) showed better antibacterial activity against Escherichia coli bacteria, compared with standard ciprofloxacin.

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